THE ROLE OF MICRONUTRIENTS IN THE IMMUNE RESPONSE TO INFECTIOUS DISEASES

A summary of a multidisciplinary meeting in Southampton, UK, cosponsored by the Wellcome Trust and the United States Agency for International Development

Public health in developing countries is influenced by both nutrition and infectious disease. Although it has been known for some 40 years that these two factors interact in complex ways (Scrimshaw, Taylor and Gordon 1995) recent research has raised important issues about the exact nature of the interaction (Chandra and Kumari 1994, Maberly et al. 1994). While researchers are faced with the challenge of applying new techniques and a better understanding of disease to improve understanding of the interplay between nutrition and infection, program designers need to apply the new knowledge to develop innovative, cost-effective and long-term programs to improve the health of underprivileged populations.

Advances in drug treatments (against bacteria, viruses, fungal pathogens and helminths) and immunization have transformed the demographic profile of developing countries. Child survival has led to a rise in life expectancy but despite three decades of progress, one child in three does not survive to adulthood. Children's health therefore remains a key priority for research and public health programs.

Studies are being undertaken on the interactions between micronutrients and infection with bacteria, viruses, or parasites. Increased vitamin A intake can reduce mortality from childhood diseases (Beaton et al. 1993, Fawzi et al. 1993, Glasziou et al. 1993). Death from measles complications in hospitalized children is also reduced by high-dose vitamin A therapy (Hussey and Klein 1990). Even maternal mortality related to childbirth may be reduced by weekly supplementation with vitamin A or beta-carotene, although the mechanism is unclear (West et al. 1999) and further studies are needed. Zinc supplementation has been suggested to decrease the incidence of persistent diarrhea in children (Roy et al. 1997, Sazawal et al. 1996). In contrast, Brunser et al. (1993) found that adding iron to complementary food for infants and young children may increase the incidence of diarrheal gastroenteritis, although this has not been confirmed (Heresi et al. 1995).

Clearly, there are gaps in our knowledge of the links between micronutrients and infection, and of the underlying immunological mechanisms. Identifying these gaps would help funding agencies refine priority areas for investment in research. Moreover, an improved understanding of these interactions would benefit donor agencies, such as the World Health Organization (WHO), Food and Agriculture Organization (FAO), United Nations Children's Fund (UNICEF), and World Food Programme (WFP), which aim to provide programmatic assistance and to promote social and economic development. These

organisations need to identify the most cost-effective options for increasing child survival. These will invariably include a combination of interventions related to environmental health, immunizations, chemotherapeutic agents that may adversely affect the intake of certain micronutrients, and nutrition and health counseling and education that result in effective behavior change.

The Organization and Charge of the Meeting

In October, 1998, a small multidisciplinary meeting was held in Southampton, UK, to discuss unresolved issues related to the interaction between micronutrients and infection. Delegates included representatives from developing and developed countries with expertise in clinical disciplines (nutrition, infectious diseases, immunology) as well as professionals from the related fields of epidemiology and medical ethics. Within the field of nutrition, participants included experts in basic nutrition and the human biology of three selected nutrients, namely vitamin A, iron, and zinc.

To provoke a maximum amount of interaction and discussion among the multidisciplinary participants, the meeting included a mixture of formats - such as plenary lectures, working-group sessions, and workshops.

The Revelations and Conclusions

Consistent with the objective to stimulate interactions between specialists in different areas of research, plenary lectures by Gerry Keusch (National Institutes of Health, USA) and George Griffin (St George's Hospital, University of London, UK) covered "Micronutrients and Acute Infections". This set the framework for the ensuing discussions on the specific propositions listed in Table 1. The major conclusions from the meeting centered on: 1) diagnosis and assessment of populations; 2) immunological mechanisms relating nutrition to infection; and 3) the ethical conduct of research into public health interventions.

Diagnosis and assessment of populations: It is widely recognized that assessments of human nutritional status are often imperfect. Cross-sectional epidemiological surveys and longitudinal intervention studies associating micronutrients with infections frequently do not include markers of nutrient status; when they do, the quality and validity of the diagnosis can often be called into question. The meeting addressed the recurrent question of whether current knowledge is clouded by limitations in the diagnosis of nutritional, immune and even infectious status.

Moreover, infection itself alters metabolism and redistributes circulating nutrients, making nutritional status difficult to determine. Participants discussed two contrasting views to explain why vitamin A, iron, and zinc concentrations decline during active infection. One view is that nutrients move preferentially from serum to tissue sites to participate in the immunological response to infection; the other is that nutrients are cleared from the circulation to deprive pathogens of the micronutrients they need for proliferation. Thus low blood micronutrient levels may not necessarily indicate a deficiency state. Correspondingly, attempts to restore normal circulating levels of micronutrients during infection may be misguided.

In terms of infection status, participants concluded it was unwise to rely on simple symptom categories without specific etiological diagnosis. The symptoms of many diseases include watery diarrhea or bloody dysentery, but not all will be equally susceptible to the same drugs. They also are unlikely to have the same associations with nutrition. How is a strong cough related to the severity of an illness? Does it reflect a more severe infection or is it the result of a more robust immune response?

Table 1: THE PROPOSITIONS FOR DISCUSSION

Single micronutrients

The observed effect of vitamin A supplementation on childhood mortality is related to the underlying nutritional deficiency: it is not a physiological effect of pharmacological doses of vitamin A.

The mechanism of therapeutic and prophylactic effects of zinc on diarrheal disease is due to local, gastrointestinal effects and not via systemic effects associated with the alleviation of underlying zinc deficiency.

Iron status determines susceptibility to – and severity of – infections.

Multiple micronutrients

There are potentially significant toxic consequences of a population-based, universal supplementation of vitamin A, zinc and iron.

Absorption and utilization of micronutrients (vitamin A, iron, zinc) are altered during infection.

The effects of multiple micronutrient supplements on infection are not independent of each other and are additive or synergistic.

The acute-phase response

The acute-phase response to infection enhances survival.

Cytokines mediate the acute-phase response's influence on vitamin A by transcriptional regulation.

Cytokines mediate the acute-phase response's influence on zinc by transcriptional regulation.

Immunological status is hampered both by the absence of suitable non-invasive techniques to assess immune status in relation to nutrition, and by a lack of understanding of the mechanistic relationships between nutrition and infection. It is critical to have measures to monitor both the activation of the acute-phase response to infection and the systemic metabolic reaction to invasion by pathogens or exposure to their toxins.

Immunological mechanisms relating nutrition to infections: The acute-phase response is affected by nutrition and immunity in acute and in chronic infections. The metabolic response to infections includes fever, anorexia, production of specific acute-phase reactant proteins, and proliferation of immune cells and antibodies; all these effects are mediated by a cascade of cytokines (Keusch 1998). Consequently, nutrients are simultaneously lost from the body, redistributed from the circulation to tissues, and blocked from utilisation. It is increasingly feasible to modify the human acute-phase response pharmacologically, with agents that either enhance or inhibit the production of all or some cytokine mediators. Moreover, various micronutrients can also affect the production of cytokines. Thus drugs or nutritional supplementation can be used during infections, but the metabolic consequences of these changes may be difficult to predict.

In a plenary session on the final day of the meeting, the importance of interactions between the infective agent, the host, and nutrition was illustrated by Melinda Beck (University of North Carolina, Chapel Hill, USA) using a new paradigm. In a murine model of Coxsackie virus cardiomyopathy, she demonstrated that the virulence of the

virus was genetically altered by the nutritional environment of the host. That is, a nonvirulent strain that was used to infect mice with antioxidant nutrient deficiencies became virulent during replication in the host. This observation provides a new dimension to the study of micronutrient-infection interactions that may achieve greater prominence in the future.

Ethical conduct of research on public health interventions: A medical ethicist (Tom Wilkie, Wellcome Trust, UK) observed the deliberations of the meeting at which the history of research design and aspirations for improving investigations, especially in developing countries, were discussed. In response to particular insights concerning the interaction between micronutrients and infection, a set of precepts evolved – that scientists have an obligation to the human volunteers participating in the research as well as their own self-respect and integrity, and that the Ethical Guidelines for Human Investigation of the WHO's Council of International Organizations of Medical Sciences (CIOMS) should be consulted and adhered to when research is carried out in developing countries.

Ethical issues permeate all aspects of research and public health programs related to micronutrients and infection. In many large clinical trials, it is unclear whether the effects of micronutrients have a nutritional or pharmacological basis. This uncertainty has important implications biologically and for public health programs, as well as practical consequences for both research donors and regulatory agencies. A drug trial involves a series of steps, with Phase 1 being an assessment of its safety, Phase 2 being an examination of its potential efficacy outside of a comparative focus and Phase 3 being a formal controlled comparative trial. If nutrients are acting principally by pharmacological mechanisms, subjecting huge populations to massive trials would need to become the last option, rather than the first. The safety aspect of the mass distribution of micronutrients is illustrated by studies of zinc intake in HIV-infected males and the progression to AIDS. Higher intakes of dietary zinc, and the use of zinc supplements were associated with a faster progression to AIDS (Tang et al. 1993) and to an earlier mortality (Tang et al. 1996).

The Future Challenges of Micronutrients and Infection Interactions

In research, the challenge is to develop better ways of resolving issues on the interaction between micronutrients such as vitamin A, iron, and zinc and viral, bacterial, and parasitic infections. These findings then need to be applied to reducing mortality and morbidity from communicable diseases in developing countries. Achieving these goals will require better technology, improved biological and epidemiological concepts, and better interdisciplinary and intersectorial communication.

Both the design and implementation of basic and applied research need to improve. In epidemiological assessments of morbidity, specific etiological diagnosis of infectious agents – rather than simple recording of infectious symptoms or syndromes – is needed to make sense of the nutrient associations. With respect to nutritional status, it needs to be clear whether low circulating levels of a nutrient reflect metabolic alterations due to infection or are true deficiency states (Underwood 1998). Complementary to this, diagnostic approaches to nutrition are needed that are not confounded by the presence of active infections. In field studies too much emphasis may have been placed on evaluating maximal response capacity rather than a more "functional" approach which recognizes that immune responses are regulated and interactive. In the three domains of infectious epidemiology, nutritional assessment, and immune status evaluation, efforts to make specimen collection procedures minimally invasive, safe and culturally acceptable are paramount. There needs to be a heightened recognition of the risks involved in all studies, and the research community must take responsibility for the health of the participants in experimental interventions.

The practice of simply noting associations between nutritional status (or nutrient administration) and infectious disease must give way to addressing the underlying mechanisms of the host immune response. One of the foremost reasons for integrating the various disciplines is to design research that is both driven by hypothesis and based on current understanding, but which also helps to fill in the gaps in knowledge of the biological mechanisms.

A fundamental premise in convening this meeting was that a lack of interdisciplinary interaction was thwarting progress towards public health solutions. Much could be gained by cross-pollinating field observations with an understanding of the mechanisms provided by basic scientists. The ultimate goal of research and aid programs is to meet the needs and expectations of at-risk populations. This will only happen if the different scientific constituencies of nutrition, immunology and infectious disease work together to inform the development of policy and public health programs. Existing programs that do not benefit the population, or do not benefit them in a cost-effective way, must be re-evaluated. Interventions which promise to reduce the prevalence of micronutrient malnutrition, or to exploit the antiinfective properties of micronutrient supplements, must be targeted at the populations who can gain the greatest benefits.

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